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(54) Title: INJECTABLE COLLAGEN–BASED DELIVERY SYSTEM FOR BONE MORPHOGENIC PROTEINS

(57) Abstract

Disclosed herein is a method for delivering a bone morphogenic protein to a tissue site, the method involving: (a) combining the bone morphogenic protein (BMP) with a soluble collagen; and (b) administering the BMP–collagen solution to the tissue site, whereby, upon contact with the tissue, the collagen solution is converted to a collagen gel. Also disclosed herein is the use of this method for treating bone or cartilage defects, as well as useful BMP–collagen solutions.

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INJECTABLE COLLAGEN-BASED DELIVERY SYSTEM FOR BONE MORPHOGENIC PROTEINS

Background of the Invention

In general, this invention relates to a delivery system for bone morphogenic proteins.

Bone is a living, dynamic tissue with substantial capacity for regeneration. Through the tightly-controlled, ongoing processes of formation and resorption, bone is involved in the regulation of serum calcium, is able to remodel in order to respond to changes in physical stress placed upon it, and is able to repair both microfractures and substantial fractures within its structure. These processes are controlled, at least in part, by the large number of growth factors present in the bone matrix. These factors include basic and acidic fibroblast growth factor, insulin-like growth factors I and II, the superfamily of transforming growth factors beta (TGFβ), platelet derived growth factors, and bone morphogenic proteins.

Originally identified as the active components within osteoinductive extracts derived from bone, the bone morphogenic proteins, or BMPs, are now known to include a large family of proteins within the TFGβ superfamily of growth and differentiation factors. Members of the BMP family have been determined to be key signaling molecules in embryogenesis, in species ranging from Drosophila to humans. They are involved in delivering positional information as well as the development of hard tissues (bones and teeth) and soft tissues. When implanted into adult animals, several of the BMPs have been shown to initiate the complex cellular process resulting in the induction of bone through both the endochondral and intramembranous bone formation

pathways. Preclinical studies have shown the ability of these factors to induce bone and heal defects in a variety of models relevant to orthopedic, oral, and maxillofacial/dental clinical problems. For example, implantation of recombinant human BMP-2 has been shown to augment the alveolar ridge in several animal models and to restore not only new bone but also tissue attachment in the periodontal environment. Results from ongoing clinical studies support the ability of recombinant human BMP-2 implants to induce physiologic bone.

Summary of the Invention

In general, the invention features a method for delivering a bone morphogenic protein to a tissue site, the method involving: (a) combining the bone morphogenic protein (BMP) with a soluble collagen; and (b) administering the BMP-collagen solution to the tissue site, whereby, upon contact with the tissue, the collagen solution is converted to a collagen gel.

In preferred embodiments, the BMP-collagen solution is administered by injection; the tissue site is bone or cartilage; the site has a defect; the defect is treated by BMP delivery; the collagen solution, upon administration to the tissue, is converted to a collagen gel within 180 seconds, more preferably, within 120 seconds, and, most preferably, within 90 seconds; the soluble collagen includes a fibrillar component and forms a fibrillar matrix; the fibrillar component is at a concentration of between 0.01-2.0%, more preferably, 0.1-0.8% (fibrillar collagen solids (w/v)); the BMP-collagen solution is at approximately pH 5.5-7.5, preferably, approximately 6.0-6.5; and the bone morphogenic protein is selected from the TGFβ superfamily, e.g., BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, osteoinductive factor (OIF), BMP-8, BMP-9, BMP-10, BMP-

12, BMP-13, and BMP-14. Preferably, the bone morphogenic protein is human BMP-2.

In a related aspect, the invention features a bone morphogenic protein (BMP)-collagen solution, whereby, upon administration to a tissue, the solution is converted to a collagen gel.

In preferred embodiments, this BMP-collagen solution is injectable; the BMP-collagen solution, upon administration to a tissue, is converted to a collagen gel within 180 seconds, more preferably, within 120 seconds, and, most preferably, within 90 seconds; the BMP-collagen solution includes a fibrillar component and forms a fibrillar matrix; the fibrillar component is at a concentration of 0.01-2.0%, more preferably, 0.1-0.8% (fibrillar collagen solids (w/v)); the BMP-collagen solution is at approximately pH 5.5-7.5, more preferably, at approximately pH 6.0-6.5; and the bone morphogenic protein is selected from the TGFβ superfamily, e.g., BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, osteoinductive factor (OIF), BMP-8, BMP-9, BMP-10, BMP-12, BMP-13, and BMP-14. Preferably, the bone morphogenic protein is human BMP-2.

By "tissue" is meant an aggregation of similarly specialized cells in an organism, preferably, mammalian, and, most preferably, human, where the cells are exposed to the organism's extracellular fluid, and are united in performance of a function within an organism.

By "fibrillar component" is meant an insoluble fibrillar collagen component wherein the collagen molecules interact in a quarter-stagger array to form microfibrils which themselves aggregate by side-to-side and end-to-end association to form stabilized collagen fibrils. The fibrillar component exhibits a collagen solid content ranging from about 0.1-2.0% (w/v) fibrillar collagen

solids.

By "fibrillar collagen solids" is meant the dry collagen solid content of the fibrillar component in terms of percent fibrillar solids. Prior to addition to a soluble collagen formulation, the collagen solids are suspended in solution at a concentration ranging from 10-100 mg/ml, preferably 40 mg/ml. The collagen solid suspension is then added to the soluble collagen formulation for a final collagen solid concentration of 0.1-2.0%, or 1-20 mg/ml.

The present invention provides a number of advantages. For example, the collagen delivery systems described herein are biocompatible, readily available, and stable in solution at neutral pH. These properties allow for the homogeneous dispersion of active BMP peptides, injectable administration of these peptides through a fine gauge needle (for example, a 30 gauge needle), sufficient density to fill a bone defect and to remain in place until gelation and fibril formation, and substantial BMP delivery for the maintenance of the active peptide in the bone matrix for a period of time sufficient to promote healing.

Other features and advantages of the invention will be apparent from the detailed description thereof and from the claims.

Description of the Drawing

FIGURE 1 is a graph demonstrating recombinant human BMP-2 retention following injection in combination with either the presently-described rapidly polymerizing collagen containing a 20% fibrillar collagen component, buffer, or a collagen sponge.

Detailed Description

Described herein is an injectable delivery system for BMPs which involves an initially soluble collagen which is capable of rapid polymerization. The low viscosity of the initial collagen solution allows homogeneous mixing of the introduced BMP and administration to a site by injection. The rapid polymerization characteristic allows for targeted delivery of the peptide to specific tissue sites and in concentrations which may be readily controlled through the choice of BMP concentration in the soluble collagen mixture.

Any collagen which exhibits the properties of an initially soluble state followed by rapid polymerization (preferably, within 180 seconds, more preferably, within 120 seconds, and, most preferably, within 90 seconds) may be used in the invention. Because this delivery system is optimally designed for use in mammalian systems, rapid polymerization preferably occurs at temperatures and pH's which approximate the physiological conditions of the recipient mammal. For humans, this collagen preferably polymerizes in a range of about 36°-39°C and at a pH of about 6.5-7.5.

Particularly preferred collagens for use in the invention are described in DeVore & Eiferman (U.S. Patent No. 5,492,135.) These collagens are initially soluble in form and, upon exposure to physiological fluids, undergo rapid polymerization. Such collagen solutions have been prepared at concentrations ranging from 10 mg/ml to over 70 mg/ml and at pH's ranging from about 6.0-8.0.

In addition, if desired, a fibrillar component may be added to the collagen solution to stabilize the BMP. Any appropriate fibrillar component may be utilized. Fibrillar collagen may be reconstituted from animal sources, such as bovine hide, using methods described, for example, in Borel and Randoux, Frontiers in Matrix Biology, Vol. 10, pages 1-58, In *Methods of*

Connective Tissue Research, Eds. Robert, Moczar, and Moczar, S. Karger, Basel, 1985. Fibrillar collagen may also be prepared from human or animal tissue sources using the method of Kelman and DeVore (U.S. Patent Nos. 4,969,912 and 5,322,802.) Concentrations of the fibrillar collagen component may range from about 0.01-2.0% (collagen solids (w/v)).

The injectable collagen systems described herein may be used to deliver any bone morphogenic protein selected from the TGFβ superfamily, including, without limitation, BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14 and osteoinductive factor (OIF). Preferably, the bone morphogenic protein is BMP-2. In each case, the protein is added to the collagen solution to a desired concentration, and the solution is administered to the appropriate tissue site. If desired, combinations of two or more BMPs may be administered simultaneously, or the BMP may be combined with other compounds which encourage bone formation, for example, hydroxyapatite, calcium phosphate, or other non-collagen materials such as coral powder. Typically, the collagen-BMP solution is administered to a site, for example, the site of a bone or collagen defect by syringe injection or surgical placement.

The injectable collagen-BMP delivery system described herein is ideally suited to the treatment and repair of bone defects (for example, injury, fracture, or non-union fracture) or cartilage defects or injury. In addition, the collagen-BMP preparation can also be applied to increase bone density in the treatment of osteoporosis.

There is described below a set of experiments demonstrating that the present injectable collagen system provides a means by which BMPs may be retained and delivered, for example, to a bone defect to promote healing

through encouragement of new bone formation. These examples are provided for the purpose of illustrating the invention and should not be construed as limiting.

Preparation of Injectable Collagen-Bone Morphogenic Protein

For delivery of bone morphogenic protein, samples of collagen were prepared from bovine corium by the methods described in DeVore and Eiferman (U.S. Patent No. 5,492,135.) Because BMP is active at slightly acidic pH, the rapidly gelling collagen was dialyzed to pH 6.0.

For all of the following experiments, recombinant human BMP-2 was used. Experiments were conducted to determine whether the addition of BMP in buffer (pH 4.5) would impede gelation or fibril formation. BMP was added to collagen at a 1:1 ratio, mixed using two syringes attached by a syringe adaptor, and then injected into a 0.8% saline solution. The still viscous mixture sank to the bottom of the solution. Gelation and fibril formation occurred within 1 minute of introduction into the saline.

The above-described collagen preparation, free of BMP, was implanted in a standard rabbit ear model. Ten day explants were examined histologically using a standard hematoxylin and eosin staining procedure as described, for example, in Luna, Specimen Preparation Pathology, pages 30-41, in *Pathology of Skin*, Eds. Farmer and Hood, Prentice Hall Int. Corp., East Norwalk, CT, 1990. The results indicated that the collagen solution had become fibrillar and had incorporated into the surrounding subcutaneous structures. There was no visible inflammation, and host fibroblasts appeared to have infiltrated the collagen matrix. These results, therefore, demonstrated the biocompatability of the collagen preparation.

In Vitro Evaluation of Collagen-BMP

Several concentrations of the soluble collagen described above were mixed with ^{125}I-BMP. The mixtures were placed in dialysis devices and incubated in physiological saline. Aliquots of incubation fluid and formed gels were then tested for ^{125}I-BMP at time intervals of up to 400 hours. Release kinetics of ^{125}I-BMP in soluble collagen and in soluble collagen plus 5% fibrillar collagen matrix (at about 40 mg/ml, resulting in 0.2% fibrillar collagen solids) were determined. This fibrillar collagen was produced by the method of Kelman and Devore (U.S. Patent Nos. 4,969,912 and 5,332,802).

These *in vitro* experiments demonstrated that a fibrillar component stabilized BMP in the rapidly polymerizing collagen formulation. A 5% fibrillar collagen matrix addition to the formulation dramatically prolonged the elution of ^{125}I-BMP. BMP release from the fibrillar collagen formulation was approximately 50% in the first 24 hours, followed by a steady-state release for up to 400 hours. In contrast, a collagen formulation lacking a fibrillar component released 70-90% of its BMP in the first 24 hours. As a result of these experiments, all subsequent collagen formulations described herein contained at least 10% fibrillar collagen matrix (at about 40 mg/ml, resulting in 0.4% fibrillar collagen solids).

In Vivo Evaluation of Collagen-BMP

Experiments were also carried out to evaluate the *in vivo* efficacy of the rapidly polymerizing collagen-BMP formulations described above. In these experiments, BMP (mixed with ^{125}I-BMP) was combined with collagen formulations containing 10% and 20% fibrillar collagen matrix (at about 40 mg/ml, resulting in 0.4% and 0.8% fibrillar collagen solids, respectively) to deliver a BMP dose of 20 µg in a 200 µl injection. Twelve rats were given 4

injections each, 2 intramuscularly and 2 subcutaneously. Six rats were included in each formulation group (that is, the 10% fibrillar and the 20% fibrillar component groups). Surgically-implanted sponges containing BMP and injections of BMP in buffer were used as non-collagen controls. Fourteen days following injection, the implant sites were removed for radiographic and histological analysis.

Following *in vivo* collagen-BMP injection, all injection sites demonstrated production of bone structure. Histologic evaluation of the ectopic explants showed the presence of well-defined nodules of woven bone organized into trabeculae and spicules. Polarizable collagen material was visible, arranged in a meshwork permeated by osteocytes randomly and unevenly distributed within the trabeculae. Osteoblastic activity with concomitant mineralization was intense. Collagen preparations with 20% fibrillar collagen appeared to produce denser bone after 14 days than did the 10% fibrillar collagen preparation.

In addition, the 20% fibrillar collagen formulation had greater BMP retention at the implantation site than did the 10% fibrillar formulation. Indeed, the 20% fibrillar collagen formulation retained 60% of the BMP retained using a surgically-implanted sponge (a standard treatment) and 150% of that retained following BMP-buffer injections. Comparative retention was consistent for up to nearly 200 hours post-implantation (Figure 1).

Rapidly polymerizing collagen formulations containing 20% fibrillar bovine collagen matrix and BMP (mixed with ^{125}I-BMP) were also injected into bone-groove defects in rabbit forelimb long bones (80 µg BMP/200 µl aliquot). Surgically-implanted sponges containing BMP and injections of BMP in buffer were used as non-collagen controls. Animals were examined radiographically at 3, 24, 47, 72, 100, 170, and 190 hours post-treatment, as well as at 2, 3, and 4

weeks post-treatment. At 4 weeks, the implant sites and surrounding bone were removed for histological examination.

These results clearly demonstrated the ability of the rapidly polymerizing collagen-fibrillar formulation to deliver BMP for the inducement of bone formation in the ectopic rat models. The denser bone formation in the collagen preparation containing a 20% fibrillar component is likely due to the greater BMP retention, and, thus, the extended duration of BMP release. Nevertheless, all formulations and all injection sites in the rat model, intramuscular and subcutaneous, exhibited bone formation. In addition, all injection sites "set-up" into gelatinous-fibrous plugs with little indication of diffusion or migration. These results indicated that this collagen-based delivery system is ideal for injectable delivery of BMP to treat bone defects.

Other Embodiments

Other embodiments are within the claims. All publications mentioned herein are hereby incorporated by reference.

What is claimed is:

Claims

1. A method for delivering a bone morphogenic protein to a tissue site, said method comprising:

(a) combining said bone morphogenic protein (BMP) with a soluble collagen; and

(b) administering said BMP-collagen solution to said tissue site, whereby, upon contact with said tissue, said collagen solution is converted to a collagen gel.

2. The method of claim 1, wherein said BMP-collagen solution is administered by injection.

3. The method of claim 1, wherein said tissue site is bone or cartilage.

4. The method of claim 3, wherein said tissue site has a defect.

5. The method of claim 4, whereby said defect is treated by delivery of said BMP to said tissue site.

6. The method of claim 1, whereby, upon administration to said tissue, said collagen solution is converted to a collagen gel within 180 seconds.

7. The method of claim 1, wherein said soluble collagen comprises a fibrillar component and forms a fibrillar matrix.

8. The method of claim 7, wherein said fibrillar component is at a concentration of about 0.01-2.0% (w/v) fibrillar collagen solids.

9. The method of claim 8, wherein said fibrillar component is at a concentration of 0.1-0.8% (w/v) fibrillar collagen solids.

10. The method of claim 1, wherein said BMP-collagen solution is at approximately pH 5.5-7.5.

11. The method of claim 10, wherein said BMP-collagen solution is at approximately pH 6.0-6.5.

12. The method of claim 1 or 10, wherein said bone morphogenic protein is selected from the superfamily of TGFβ cytokines comprising BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, and osteoinductive factor (OIF).

13. The method of claim 12, wherein said bone morphogenic protein is human BMP-2.

14. A bone morphogenic protein (BMP)-collagen solution, whereby, upon administration to a tissue, said solution is converted to a collagen gel.

15. The BMP-collagen solution of claim 14, wherein said BMP-collagen solution is injectable.

16. The BMP-collagen solution of claim 14, whereby, upon

administration to said tissue, said collagen solution is converted to a collagen gel within 180 seconds.

17. The BMP-collagen solution of claim 14, wherein said solution further comprises a fibrillar component and forms a fibrillar matrix.

18. The BMP-collagen solution of claim 17, wherein said fibrillar component is at a concentration of between 0.01-2.0% (w/v) fibrillar collagen solids.

19. The BMP-collagen solution of claim 18, wherein said fibrillar component is at a concentration of approximately 0.1-0.8% (w/v) fibrillar collagen solids.

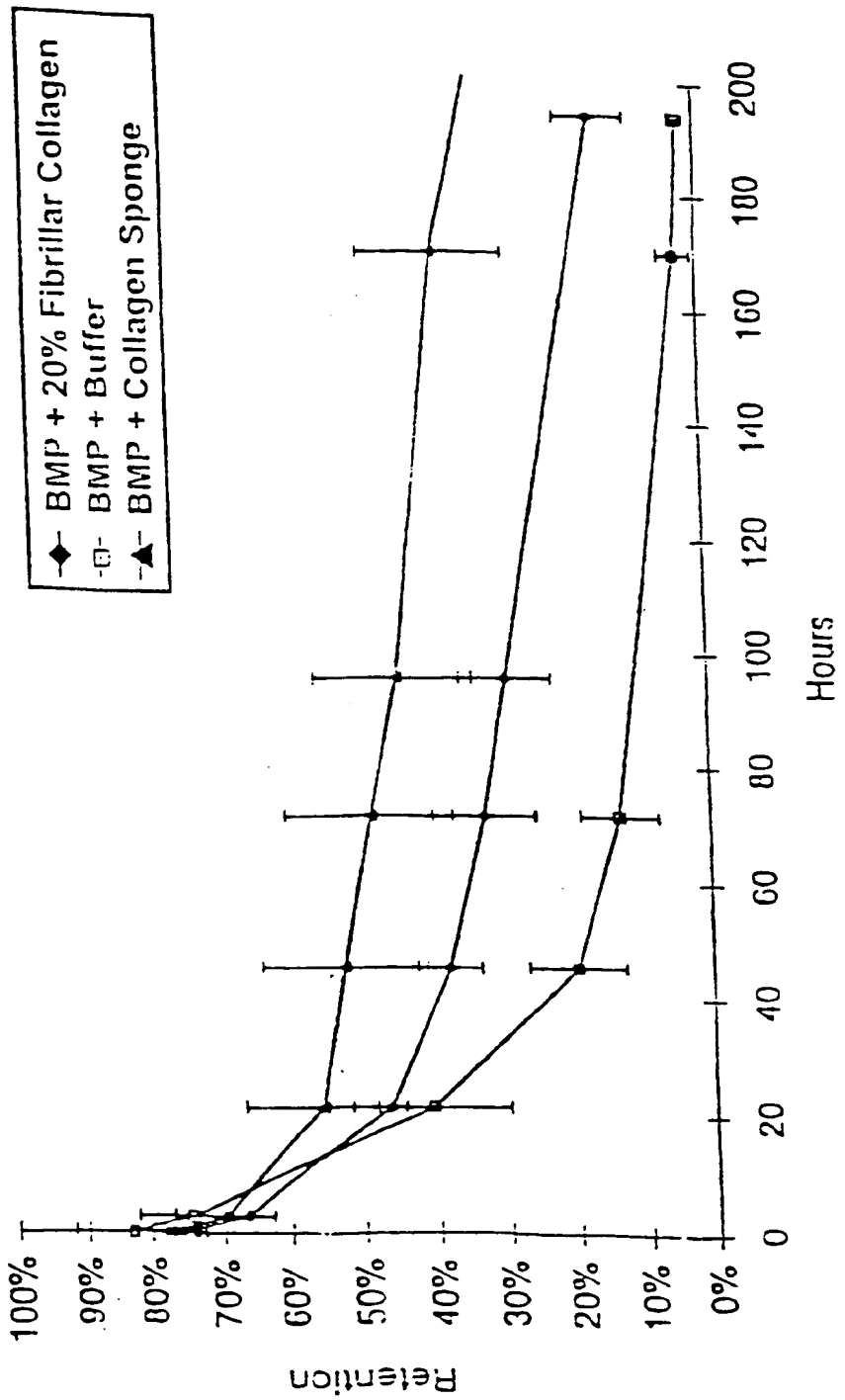
20. The BMP-collagen solution of claim 14, wherein said solution is at approximately pH 5.5-7.5.

21. The BMP-collagen solution of claim 20, wherein said solution is at approximately pH 6.0-6.5.

22. The BMP-collagen solution of claim 14 or 20, wherein said bone morphogenic protein is selected from the superfamily of TGFβ cytokines comprising BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7 and osteoinductive factor (OIF).

23. The BMP-collagen solution of claim 22, wherein said bone morphogenic protein is human BMP-2.

FIGURE 1



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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61B 17/00; A61K 38/18
US CL :128/898; 522/68; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 522/68; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST (US patents); DIALOG (biotech files)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,492,135 A (DEVORE et al) 20 February 1996, see entire document.	1-23
Y,E	US 6,039,762 A (MCKAY) 21 March 2000, see entire document.	1-23
Y,P	US 6,007,833 A (CHUDZIK et al) 28 December 1999, see entire document.	1-23
Y	US 5,475,052 A (RHEE et al) 12 December 1995, see entire document.	1-23
Y	US 5,413,989 A (OGAWA et al) 09 May 1995, see entire document.	1-23
Y	US 4,975,527 A (KOEZUKA et al) 04 December 1990, see entire document.	1-23

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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INTERNATIONAL SEARCH REPORT

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PCT/US00/03151

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,674,292 A (TUCKER et al) 07 October 1997, see entire document.	1-23

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